

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: H. Michael SHEPARD  
Title: METHODS FOR TREATING  
THERAPY-RESISTANT  
TUMORS

Appl. No.: 10/048,033

International 7/21/2000  
Filing Date:  
371(c) Date:

Examiner: Crane, Lawrence E.

Art Unit: 1623

Confirmation 2767  
Number:

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August 30, 2007  
(Date of Transmission)

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 CFR §1.56**

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicants  
in order to comply with Applicants' duty of disclosure pursuant to 37 CFR §1.56.

A copy of each non-U.S. patent document and each non-patent document is being  
submitted to comply with the provisions of 37 CFR §1.97 and §1.98.

The submission of any document herewith, which is not a statutory bar, is not intended as  
an admission that such document constitutes prior art against the claims of the present  
application or that such document is considered material to patentability as defined in 37 CFR

§ 1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a *prima facie* art reference against the claims of the present application.

### **TIMING OF THE DISCLOSURE**

The listed documents are being submitted in compliance with 37 CFR § 1.97(c), before the mailing date of either a final action under 37 CFR § 1.113, a notice of allowance under 37 CFR § 1.311, or an action that otherwise closes prosecution in the application.

### **RELEVANCE OF EACH DOCUMENT**

U.S. Patent Reference #1 (6,589, 941) is the equivalent of foreign-language reference #15 (WO 96/23506). An English translation of the foreign-language document is not readily available. However, the absence of such translation does not relieve the PTO from its duty to consider the submitted foreign language document (37 CFR § 1.98 and MPEP § 609).

Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP § 609.

### **FEE**

Fees in the amount of \$180.00 in accordance with 37 CFR § 1.17(p) to cover the fee associated with an information disclosure statement under 37 CFR § 1.97(c) are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

Date

Aug. 30, 2007

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By

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Substitute for form 1449/PTO  
**INFORMATION DISCLOSURE  
 STATEMENT BY APPLICANT**

Date Submitted: August 30, 2007

(use as many sheets as necessary)

**Complete if Known**

Application Number	10/048033
Filing Date	7/21/2000
First Named Inventor	H. Michael Shepard
Art Unit	1623
Examiner Name	Crane, Lawrence E.
Attorney Docket Number	060925-0601

Sheet 2 of 5

**NON PATENT LITERATURE DOCUMENTS**

Examin or Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>6</sup>
	D16	BALZARINI et al. "Highly Selective Cytostatic Activity of (E)-5-(2-Bromovinyl)-2'-deoxyuridine Derivatives for Murine Mammary Carcinoma (FM3A) Cells Transfected with the Herpes Simplex Virus Type 1 Thymidine Kinase Gene" Molecular Pharmacology (1985) 28:581-587	
	D17	BALZARINI et al. "The cytostatic activity of 5-(1-azidovinyl)-2'-deoxyuridine (AzVDU) against herpes simplex virus thymidine kinase gene-transfected FM3A cells is due to inhibition of thymidylate synthase and enhanced by UV light ( $\lambda = 254$ nm) exposure" FEBS Lett. 373:41-44 (1995)	
	D18	BARBATO et al. "Synthesis of bridged pyrimidine nucleosides and triazo [4, 3-c] pyrimidine nucleoside analogues" Nucleosides & Nucleotides 8(4):515-528 (1989)	
	D19	BATHE et al. "Increased thymidylate synthase gene expression in liver metastases from colorectal carcinoma: Implications for chemotherapeutic options and survival" Cancer J. Sci. Am. 5(1):34-40 (1999)	
	D20	BIBLE et al. "Cytotoxic synergy between flavopiridol (NSC 649890, L86-8275) and various antineoplastic agents: the importance of sequence of administration" Cancer Res. 57(16):3375-80 (August 15, 1997)	
	D21	BRONZERT, D.A. "Purification and Properties of Estrogen-responsive Cytoplasmic Thymidine Kinase from Human Breast Cancer" Can. Res. (Feb. 1981) 41:604-610	
	D22	CASS et al. "Recent advances in the molecular biology of nucleoside transporters of mammalian cells" Biochem. Cell Biol. 76(5):761-770 (1998)	
	D23	CHOU and TALALAY, "Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors" Adv. Enzyme Regul. 22:27-55 (1984)	
	D24	CORDON-CARDO and PRIVES "At the crossroads of inflammation and tumorigenesis" J. Exp. Med. 190(10):1367-1370 (November 15, 1999)	
	D25	COSTI et al. "Phthalin derivatives as a new tool for selectivity in thymidylate synthase inhibition" J. Med. Chem. 42(12):2112-2124 (1999)	
	D26	COSTI, et al. "Thymidylate Synthase Inhibition: A Structure-Based Rationale for Drug Design" Medical Research Review 18(1):21-42 (1998)	
	D27	CURT "Cancer drug development: new targets for cancer treatment" Oncologist 1(3):II-III (1996)	

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Substitute for form 1449/PTO		<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>		<b>Application Number</b>	10/048033
Date Submitted: August 30, 2007		<b>Filing Date</b>	7/21/2000
<i>(use as many sheets as necessary)</i>		<b>First Named Inventor</b>	H. Michael Shepard
		<b>Art Unit</b>	1623
		<b>Examiner Name</b>	Crane, Lawrence E.
		<b>Attorney Docket Number</b>	060925-0601
Sheet	3	of	5

## NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. 1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>6</sup>
	D28	DeCLERCQ et al. "Antiviral Activity of Novel Deoxyuridine Derivatives" Current Chemotherapy: Proceedings of the International Congress of Chemotherapy 1:352-354 (September 18, 1978)	
	D29	DeCLERCQ "Antiviral Activity Spectrum and Target of Action of Different Classes of Nucleoside Analogues" Nucleosides & Nucleotides 13(6&7):1271-1295 (1994)	
	D30	DeCLERCQ "In search of a selective antiviral chemotherapy" Clin. Micro. Review 10(4):674-693 (October 1997)	
	D31	DRAKE et al. "Resistance to Tomudex (ZD1694): Multifactorial in Human Breast and Colon Carcinoma Cell Lines" Biochem. Pharmacol. 51(10):1349-1355 (1996)	
	D32	FARROW et al. "Synthesis and biological properties of novel phosphotriesters: A new approach to the introduction of biologically active nucleotides into cells" J. Med. Chem. 33(5):1400-1406 (1990)	
	D33	GREM "Biochemical modulation of fluorouracil by dipyrindamole: preclinical and clinical experience" Semin Oncol. 19(2 Suppl 3):56-65 (April 1992)	
	D34	GRIENGL et al. "Phosphonoformate and phosphonoacetate derivatives of 5-substituted 2'deoxyuridines: Synthesis and antiviral activity" J. Med. Chem. 31(9):1831-1839 (1988)	
	D35	HENGSTSCHLAGER, M. and E. WAWRA "Cytofluorometric determination of thymidine kinase activity in a mixture of normal and neoplastic cells" Br. J. Cancer (1993) 67:1022-1025	
	D36	JOHNSTON et al. "Thymidylate synthase gene and protein expression correlate and are associated with response to 5-fluorouracil in human colorectal and gastric tumors" Cancer Res. 55:1407-1412 (1995)	
	D37	KOMAKI et al. "Difference in thymidylate synthetase activity in involved nodes compared with primary tumor in breast cancer patients" Breast Cancer Res. Treat. 35(2):157-162 (1995)	
	D38	LEICHMAN "Thymidylate synthase as a predictor of response" Oncol. 12(8Suppl.6):43-47 (August 1998)	
	D39	LIBRA, et al. "Thymidylate synthase mRNA levels are increased in liver metastases of colorectal cancer patients resistant to fluoropyrimidine-based chemotherapy" BMC Cancer 4:11 (2004)	
	D40	LIVINGSTON et al. "Studies with tetrahydrohomofolate and thymidylate synthetase from amethopterin-resistant mouse leukemia cells" Biochem. 7(8):2814-2818 (1968)	

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	D41	LOOK et al. "Increased thymidine kinase and thymidylate synthase activities in human epithelial ovarian carcinoma" Anticancer Res. 17:2353-2356 (1997)	
	D42	MIAO et al. "A Stepwise One Pot Synthesis of Alkyl Thiophosphoramidate Derivatives of Nucleosides" Synthetic Communications 32(8):1159-1167 (2002)	
	D43	NICULESCU-DUVAZ et al. "Gene-directed enzyme prodrug therapy: A review of enzyme/prodrug combinations" Expert Opin. Invest. Drugs 6(6):685-703 (1997)	
	D44	PATTERSON et al. "Thymidine phosphorylase moderates thymidine-dependent rescue after exposure to the thymidylate synthase inhibitor ZD1694 (tomudex) in vitro" Cancer Res. 58:2737-2740 (1998)	
	D45	PEDERSEN-LANE et al. "High-level expression of human thymidylate synthase" Protein Expression and Purification 10:256-262 (1997)	
	D46	ROONEY et al. "Comparative Genomic Hybridization Analysis of Chromosomal Alterations Induced by the Development of Resistance to Thymidylate Synthase Inhibitors" Cancer Res. 58:5042-5045 (November 15, 1998)	
	D47	SMITH et al. "Response to doxorubicin of cultured normal and cancerous human mammary epithelial cells" J. Nat'l Cancer Inst. 74(2):341-347 (1985)	
	D48	TOUROUTOGLOU et al. "Thymidylate synthase inhibitors" Clin. Cancer Res. 2(2):227-243 (February 1996)	
	D49	TSAVARIS et al. "Multimodal biochemical modulation of 5-fluorouracil activity in advanced colorectal cancer with allopurinol, folic acid and dipyridamol" J. Chemother. 2(2):123-126 (1990)	
	D50	van LAAR "Therapeutic efficacy of fluoropyrimidines depends on the duration of thymidylate synthase inhibition in the murine colon 26-B carcinoma tumor model" Clin. Cancer Res. 2(8):1327-1333 (1996)	
	D51	van TRIEST et al. "Thymidylate synthase level as the main predictive parameter for sensitivity to 5-fluorouracil, but not for folate-based thymidylate synthase inhibitors, in 13 nonselected colon cancer lines" Clin. Cancer Res. 5(3):643-654 (1999)	
	D52	VLAYKAVA et al. "Increased Thymidylate Synthase Gene Expression in Metastatic Melanoma" Oncology 54:146-152 (1997)	
	D53	WHALEN et al. "Human glutathione S-transferases" Seminars in Liver Disease 18(4):345-358 (1998)	

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[illegible]

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